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A STOMACH LESION IN GUINEA-PIGS CAUSED BY DIPHTHERIA TOXIN AND ITS BEARING UPON EXPERIMENTAL GASTRIC ULCER.*

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GUINEA-PIGS dying acutely from injections of diphtheria toxin frequently show a lesion in the stomach which, so far as we know, has not been described.

Our attention was first called to the condition of the stomachs of guinea-pigs used in our diphtheria work by Assistant Surgeon A. M. Stimson of the Public Health and Marine Hospital Service, in the summer of 1905. Since that time we have collected from our autopsy records 2,882 protocols in which the condition of the stomach was noted. Of these 1,897 guinea-pigs, or 66 per cent, showed the lesion in the stomach described in this paper.

In the many thousand autopsies upon guinea-pigs used in this Laboratory in preparing the standard unit for measuring the strength of diphtheria antitoxin and also for verifying the potency of the antidiphtheric serum made by licensed manufacturers, we constantly see the lesions usually found in animals dying from diphtheria poisoning, such as darkened and congested adrenals, effusions into the

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pleuræ, and other serous cavities, local edema, necrosis and hemorrhagic reaction at the site of inoculation, etc.; but it is difficult for us to understand how the condition of the mucosa of the stomach, which is so very evidently present in such a large proportion of the guinea-pigs, has escaped the observation of others.

This lesion may assume practical importance in view of the light it may throw upon experimental gastric ulcer.

The experimental production of gastric ulcer, has met with little success. The following table of experiments by previous investigators, taken from Turck's article[1] upon ulcer of the stomach gives in condensed form the method used and results obtained.

Turck, in following the subject further, has succeeded in producing ulcers of the stomach and duodenum in dogs by feeding *B. coli* for a variable length of time and as a result of his work considers that we now have, for the first time, a firm basis upon which to solve the final or underlying etiology of gastric ulcer.

In connection with the lesion in guinea-pigs which we describe it is interesting to note that Turck attempted the production of gastric ulcer in dogs by the injection of diphtheria toxin into the stomach wall. This, it seemed, did not produce an ulcer, but pinhead hemorrhagic foci in the duodenum or local necroses near the pylorus. When the diphtheria toxin is injected into the mesenteric vessels Turck also failed to produce ulcer, but obtained necroses in two weeks in the duodenum and near the pylorus.

We find that gastric ulcer may be produced in the guinea-pig by the subcutaneous inoculation of diphtheria toxin given in sufficient quantity to cause the acute death of the animal. It follows injections of a minimal lethal dose, as well as the injection of the toxin-antitoxin mixture (L + dose) used in measuring the strength of diphtheria antitoxin. When the toxin is completely neutralized by the antitoxin, as in the case of the L° mixture, and the animal afterward killed, the stomach shows no lesion.

The lesion is caused by infection with the diphtheria bacillus as well as injections of the diphtheria toxin. We injected a number of guinea-pigs with a young agar culture of *B. diphtheriae* well washed to free it from toxin. The animals sickened and died in from four to

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[1] *Jour. Am. Med. Assoc.*, 1906, 46, p. 1753.

TABLES OF EXPERIMENTS BY PREVIOUS INVESTIGATORS.

Investigator	Method	Result
A. Mechanical and Physical Injury—		
Ritter	Violent bruises	
Decker	Heat	Ulcer
Matthes	Trauma (with 5 per cent HCl)	Ulcer
Schmidt	Trauma (with HCl)	
Körte	Pinching stomach with clamps	Ulcer
B. Chemical—		
Roth	Crystals of nitrate of silver introduced into stomach	Ulcer
1. HCl as a necessary factor—		
Riegel	HCl necessary	
Matthes	Trauma (without HCl)	Negative
	Trauma (with 5 per cent HCl)	Ulcer
Schmidt	HCl and trauma	
Ewald	HCl essential factor	
2. Contra HCl—		
Pawlow	Hyperacidity a consequence	
Du Misinl	Superacidity without significance	
Ageron	HCl may be persistently absent	
Kavetsky	Synchronous ulcer of the stomach and bladder	
C. General Dysemia—		
Virchow	Anemia and chlorosis	
Quincke and Daetwyler	Anemia by producing gradual hemorrhage and local trauma	Ulcer which healed with difficulty
Silbermann	Hemoglobinemia	Ulcer
Futterer	"	Ulcer
Cohnheim	" by mechanical injury and injection of laked blood	Ulcers
D. Disturbance of Local Circulation—		
Virchow	Embolism, thrombi, aneurism or varicose veins	
Klebs and Welti	Thrombi	
Panum	Injection of emulsion of wax into femoral vein	Gastric infarcts, ulcer
Talma	Ligation of esophagus and pylorus	Ulcer
Rindfleisch	Venous stasis; prolonged ischemia	
Axel Key	Prolonged ischemia due to contraction of gastric muscle	No experiments
Müller	Tied portal vein	Ulcer
E. Injuries to Nerves and Nerve Centers—		
Schiff	Intersection of thalami and peduncles	Ulcer
Ebstein		
Brown-Sequard	Anterior corp. quadrigemina	Ulcer
Vidova	Injection of alcohol into vagus	Negative
Vidova	Section of the sympathetic	Ulcer
Yzeren	Section of the sympathetic with section of vagi below the diaphragm	Ulcer
Saitta	Section of the sympathetic with section of vagi below the diaphragm	Ulcer
Ophüls	Section of the sympathetic with section of vagi below the diaphragm	Ulcer
Koch and Ewald	Section of cord and 5 per cent HCl in stomach	Ulcer
F. Local Infection—		
Cohnheim	Injection. Infected suspensions of lead chromate	Erosions and ulcers
Böttcher	Infection as cause of ulcer	Opposed by Körte
Nauwerck	Infection observed at edge of ulcer	

six days. The autopsy findings, so far as the stomach was concerned, were precisely similar to that seen in animals dead of toxin injections.

So far as we know a similar condition of the stomach in human diphtheria has not been noted.

The lesion in the stomach of the guinea-pig consists of a sharply defined area of congestion, hemorrhage, or ulceration near or at the pyloric extremity. Occasionally the lesion extends half an inch into the duodenum and in a few instances the duodenum itself shows slight injection or congestion while the stomach remains normal.

The first stage consists principally of a congestion, always in the neighborhood of the pylorus. This is best seen in guinea-pigs dying as a result of overpowering doses of diphtheria toxin in about 24 hours. When the guinea-pig dies later, for instance on the second, third, or fourth day, the lesion is more advanced and consists of hemorrhages into the mucosa followed by destruction of tissue, sometimes extending into the muscularis, but in no case has perforation been observed.

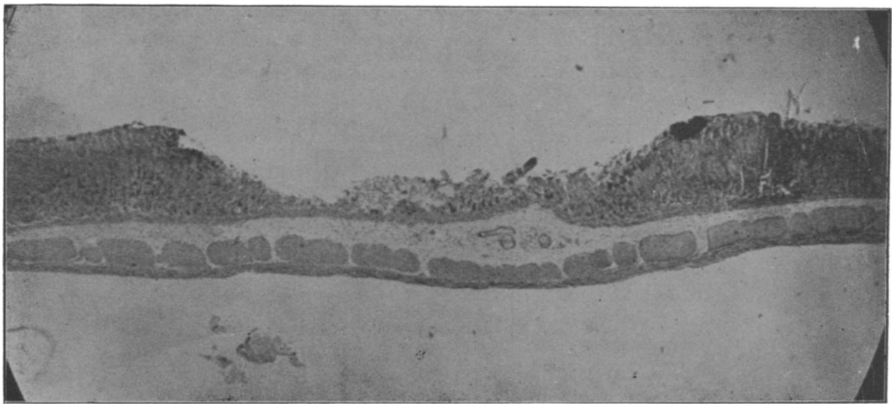

Fig. 1.—Ulcer. Note the absence of cellular infiltration, including digestion of mucosa.

It is interesting to know whether guinea-pigs that received less than a lethal dose of the diphtheria poison from which they ultimately recover may have had this stomach lesion. In a few instances in our guinea-pigs which died on the 22d and 28th days with paralysis we found old blood-stained areas in the mucosa of the stomach in the region of the pylorus indicating a healed area.

This lesion is not the result of any particular diphtheria toxin, as we have found that it follows the injection of all the various diphtheria toxins, some 25 in number, used in this laboratory.

There is no relation between the source of the guinea-pig and the effects of the diphtheria toxin, for we have found this lesion in guinea-pigs obtained from four outside sources as well as those raised in the laboratory.

We have examined a number of healthy guinea-pigs from our stock in order to assure ourselves that no other cause than the diphtheria toxin could possibly account for the appearances that we find in the stomachs of these animals.

It will be seen from the following table that when guinea-pigs are given an injection of diphtheria toxin sufficient to kill them within 24 hours, about half the animals show this lesion. When they die on the third or fourth day a very much larger proportion of the animals show the lesion. About 75 per cent of the guinea-pigs dying between the fourth and fifth days show this lesion; but in guinea-pigs dying later than the 10th day the relative number of animals showing this stomach lesion gradually diminishes. Guinea-pigs dying of late paralysis practically never showed the stomach lesion.

THE FREQUENCY WITH WHICH GUINEA-PIGS, DEAD OF DIPHTHERIA TOXIN, SHOW THE STOMACH LESION.

Time of Death	Condition of Stomach	No.	Per Cent Lesions
Less than 1 day	lesion	7	54
	normal	6	
Between 1 and 2 days	lesion	104	62
	normal	61	
" 2 " 3 "	lesion	833	77
	normal	235	
" 3 " 4 "	lesion	725	73
	normal	254	
" 4 " 5 "	lesion	163	52
	normal	144	
" 5 " 6 "	lesion	35	28
	normal	85	
" 6 " 10 "	lesion	28	25
	normal	84	
More than 10 days	lesion	2	1.7
	normal	116	
Totals	Stomach lesion	1,897	Average: 66
	" normal	985	
		2,882	

CONTROLS.

A number of comparisons were made with tetanus toxin and various chemical poisons, but in no instance was there found any similar sharply defined lesion in the pyloric extremity of the stomach.

The stomachs of a number of guinea-pigs dead of tetanus toxin appeared quite normal.

The stomachs of guinea-pigs dying acutely from strong poisons, such as hydrocyanic acid, chloralcyanhydrin, etc., sometimes show acute hemorrhagic areas either of a diffuse or punctate nature, but in such cases the lesion is not confined to the pyloric end of the stomach.

For the effect of various chemical poisons upon the stomach of guinea-pigs we are indebted to Dr. Reid Hunt, Chief of the Division of Pharmacology, Hygienic Laboratory, for the following data upon animals used by him in other lines of research and which serve as our controls:

Hydrocyanic acid.—Five guinea-pigs were given subcutaneously from 0.005 to 0.006 mg. of hydrocyanic acid, per gram of guinea-pig, which caused death in 1 hour 15 minutes to 6 hours 25 minutes.

G.-P. No. 315 (0.005 mg.): Mucosa and submucosa of anterior and posterior walls of stomach showed large acute hemorrhagic areas. Pylorus apparently normal.

G.-P. No. 305 (0.0052 mg.). Stomach showed intense hemorrhage into the mucous membrane. Pylorus apparently normal.

G.-P. No. 340 (0.0055 mg.). Mucous membrane of whole of stomach and submucosa intensely hemorrhagic.

G.-P. No. 327 (0.006 mg.). Enormous punctate hemorrhagic areas on mucous membrane of greater curvature of stomach.

G.-P. No. 365 (0.005 mg.). Mucosa of stomach slightly injected and hemorrhagic.

Chloralcyanhydrin.—Eight guinea-pigs were injected subcutaneously with chloralcyanhydrin in quantities varying from 0.0052 to 0.02 mg. per gram, which caused the death of the animals in from 6 hours to 16 minutes. The stomach in each case was normal excepting in the two animals receiving the large amounts, as follows:

G.-P. No. 330 (0.025 mg.). Acute hemorrhage of the posterior and inferior walls of the stomach, involving both the mucosa and the serous coats.

G.-P. No. 325 (0.03 mg.). Stomach shows numerous hemorrhagic areas.

Strophanthin.—Four guinea-pigs were injected subcutaneously with strophanthin in amounts varying from 0.001 to 0.005 mg. per gram, causing the death of the animals in 1 hour 35 minutes to 43 minutes. In each case the stomach appeared normal.

Strychnin sulphate.—Ten guinea-pigs were injected subcutaneously with strychnin sulphate, and others with strychnin sulphate plus alcohol. The amount of strychnin varied from 0.004 mg. to 0.005 mg. per gram, which caused the death of the animals in 11

PLATE I.

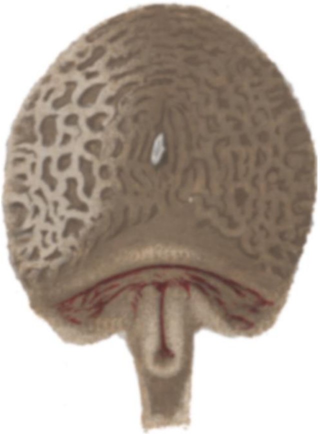

FIG. 1.

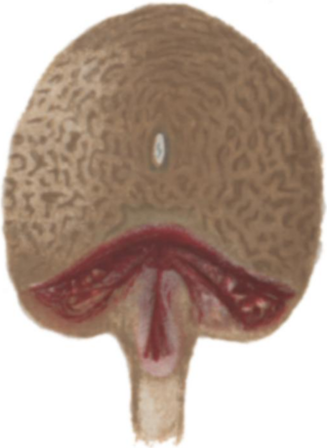

FIG. 2.

minutes to 4 hours 20 minutes. The stomach was normal in each instance.

Nitroprussiate of soda.—Three guinea-pigs were injected with amounts of nitroprussiate of soda varying from 0.015 to 0.018 mg. per gram, which caused the death of the animals in 1 hour 15 minutes to 2 hours 15 minutes. The stomach was normal in each instance.

EXPLANATION OF PLATE 1.

FIG. 1.—Stomach of guinea-pig showing mild grade of diphtheria lesion.

FIG. 2.—Stomach of guinea-pig showing severer grade, with hemorrhages and ulceration. Note the sharp line of demarkation and limitation of the pyloric extremity.